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Original Article

Effects of a high-fat diet on the electrical properties of porcine atria

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ABSTRACT

Background: Because obesity is an important risk factor for atrial fibrillation (AF), we conducted an animal study to examine the effect of a high-fat diet (HFD) on atrial properties and AF inducibility.
Methods: Ten 8-week-old pigs (weight, 18–23 kg) were divided into two groups. For 18 weeks, five pigs were fed a HFD (HFD group) and five were fed a normal diet (control group). Maps of atrial activation and voltages during sinus rhythm were created for all pigs using the EnSite NavX system. Effective refractory period (ERP) and AF inducibility were also determined. When AF was induced, complex fractionated atrial electrogram (CFAE) mapping was performed. At 18 weeks, hearts were removed for comparing the results of histological analysis between the two groups. Body weight, lipid levels, hemodynamics, cardiac structures, and electrophysiological properties were also compared.
Results: Total cholesterol levels were significantly higher (347 [191–434] *vs.* 81 [67–88] mg/dL, $P=0.0088$), and left atrium pressure was higher (34.5 [25.6–39.5] *vs.* 24.5 [21.3–27.8] mmHg, $P=0.0833$) in the HFD group than in the control group, although body weight only increased marginally (89 [78–101] *vs.* 70 [66–91] kg, $P=0.3472$). ERPs of the pulmonary vein (PV) were shorter ($P<0.05$) and AF lasted longer in the HFD group than in the control group (80 [45–1350] *vs.* 22 [3–30] s, $P=0.0212$). Neither CFAE site distribution nor histopathological characteristics differed between the two groups.
Conclusions: The shorter ERPs for the PV observed in response to the HFD increased vulnerability to AF, and these electrophysiological characteristics may underlie obesity-related AF.

1. Introduction

Metabolic syndrome comprises a cluster of conditions, including obesity, insulin resistance, hypertension, and abnormal cholesterol levels, which together increase cardiovascular risk. Metabolic syndrome and obesity have been reported to promote systemic inflammation and oxidative stress [1,2], and patients with metabolic syndrome have increased epicardial adipose tissue volumes [3]. The systemic and local conditions related to obesity and metabolic syndrome have been linked to the pathogenesis of atrial fibrillation (AF) [4–6]. In fact, numerous epidemiological studies have shown that obesity, one of the components of metabolic syndrome, is associated with both the new onset and progression of AF [7–9]. However, the mechanism explaining the link between obesity or metabolic syndrome and AF progression is unclear. To elucidate this mechanism, we investigated electrophysiological properties and vulnerability to AF in pigs fed on a high-fat diet (HFD).

2. Material and methods

2.1. Animal preparation

The experimental protocol was approved by the Institutional Animal Care and Use Committee of the Nihon University School of Medicine. Ten 8-week-old domestic pigs (weight, 18–23 kg) were divided into two groups. Five pigs were fed a normal diet for 18 weeks (control group) and five were fed a HFD for 18 weeks (HFD group). The pigs were housed in individual cages (1.25 m^3) under

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controlled conditions (23 ± 0. 5 °C, 55 ± 5% humidity, and 12 h of light from 06:00 to 18:00). The animals in the control group were fed a commercial diet (PiguMiral CEX, JA Higashinihon Kumiai Shiryou, Co., Ltd., Gunma, Japan), which consisted of 71% cereal, 12% vegetable-origin oilseed, 6% chaff and bran, and 11% vitamins and minerals. The animals in the HFD group were fed a HFD, which consisted of 25% lard, 2.5% cholesterol, 20% granulated sugar, and 52.5% commercial feed (described above). In both groups, the daily food volume intake was 1 kg from week 8 to week 10, and 2 kg from week 11 to week 18. End-study (18-week) body weight, systolic and diastolic blood pressure, heart rate, and mean left atrial pressure were obtained from all animals. Blood samples were taken, and lipids were assessed by a commercial laboratory (SRL, Inc., Tokyo, Japan). In preparation for intracardiac echocardiography (ICE) and electrophysiology study (EPS) assessments, the animals were anesthetized with an intramuscular injection of 0.1 mg/kg midazolam, which was followed by inhalation of 5% isoflurane and then 1–3% isoflurane for maintenance. A tracheal cannula was inserted, and intermittent positive-pressure ventilation (room air, tidal volume, 10 mL/kg; rate, 20 breaths/min) was provided using a respirator. After deep anesthesia was established, vascular access was obtained percutaneously via the right external jugular vein and the right and left femoral veins and artery. Surface electrocardiograms (ECGs) and blood pressure were monitored continuously throughout the procedures. A 7-Fr catheter was positioned in the distal coronary sinus (CS) for anatomical guidance, and to provide a reference for the timing of data acquisition. A 10-Fr, 64-element, 5.5–10.0-MHz, phased-array ICE catheter, which works with the Vivid 7 system (GE Healthcare Technologies, Wauwatosa, WI, USA), was advanced to the level of the tricuspid annulus to measure the left atrium (LA) and left ventricle (LV), and to guide transseptal catheterization.

2.2. ICE

ICE was performed before EPS. All recordings were taken in sinus rhythm (SR). The short and long axes of the LA were measured from a 2-dimensional (2D) ICE image (long-axis view); the LV ejection fraction, LV end-systolic and diastolic dimensions, and interventricular septum and posterior wall dimensions were also measured from the 2D ICE image (short-axis view).

2.3. EPS

Transseptal catheterization was accomplished under fluoroscopic and ICE guidance. After transseptal puncture, left atrial pressure was measured, and an Agilis deflectable long sheath (St. Jude Medical, Inc., St. Paul, MN, USA) was inserted into the LA. The 3-dimensional (3D) geometry of the right atrium (RA), LA, and four pulmonary veins (PVs) was reconstructed using the EnSite NavX system, version 8.0 (St. Jude Medical, Inc.). A 20-pole circular mapping catheter with 1.5-mm interelectrode spacing (Livewire Spiral HP Catheter, St. Jude Medical, Inc.) and 8-pole mapping catheter with 4-mm interelectrode spacing (Snake, Japan Lifeline, Inc., Tokyo, Japan) were used for the mapping and creation of the 3D geometry. A 3D activation map was created during the acquisition of bipolar signals (filter setting, 30–500 Hz) from the 20-pole circular mapping catheter. Electrograms recorded during SR were stored and analyzed offline with the NavX mapping system. Bipolar voltage amplitudes derived from two to three mapping points were averaged for each of the following 13 LA/PV segments: superior vena cava (SVC); SVC–RA junction; right atrial appendage (RAA); lateral and septal RA; septal and posterior LA and LA roof; mitral isthmus; left atrial appendage (LAA); and the orifices of the right and left superior PVs and common inferior PVs. Potentials with amplitudes >0.5 mV were deemed normal-voltage potentials and coded in purple, and potentials with amplitudes <0.2 mV were deemed low-voltage potentials and coded in red or grey [10]. The effective refractory period (ERP) (longest premature coupling interval [S1–S2] that failed to capture) was measured from both atria ($2\times$ threshold current, 2-ms pulses) at basic cycle lengths of 400 ms with eight basic stimuli (S1), followed by premature (S2) stimuli in 10-ms decrements. ERPs were obtained at six different locations (the RAA, SVC–RA junction, LAA, and orifices of the right and left superior PVs and common inferior PVs). At each site, the ERP was measured three times and averaged. AF was induced by 5-s burst pacing (10 Hz; $4\times$ threshold current), and the duration of sustained AF was measured. If AF lasting >30 s was induced repeatedly, a complex fractionated atrial electrogram (CFAE) map was created during AF. For CFAE analysis, the NavX mapping parameters were set to the CFAE-mean, an algorithm was used to determine the average index of the fractionation at each site, and a color map of the fractionation intervals (FIs) (CFAE map) was constructed [11–13]. The FI was taken as the average time between consecutive deflections over a 5-s recording period. The settings included a refractory period of 30 ms (adjusted for animals from the clinical setting of 40 ms), peak-to-peak sensitivity between 0.05 mV and 0.1 mV, and an electrogram duration of <10 ms. Continuous CFAEs were defined as those with a mean FI of <50 ms and variable CFAEs as those with an FI of 50–120 ms.

2.4. Histopathological analysis

After ICE and EPS, all animals were euthanized and their hearts were removed, fixed in 10% formalin, and subjected to histological analysis. Paraffin-embedded specimens were serially sectioned as 4-μm slices for staining with hematoxylin–eosin and Masson's trichrome. The sections were examined for fibrotic or inflammatory changes or myocyte hypertrophy present at the SVC–RA junction, RAA, lateral RA, posterior LA, LA roof, LAA, and the orifices of the right and left superior PVs and common inferior PVs. An expert pathologist (M.M.) twice interpreted at least one or two slides.

2.5. Statistical analysis

Continuous variables were expressed as median values with interquartile ranges. Between-group differences in continuous variables were analyzed using the Mann–Whitney *U* test. A *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed with JMP 11. 2.0 software (SAS Institute Inc., Cary, NC).

3. Results

3.1. End-study body weight and hemodynamic variables, ICE measurements, and lipid levels

Animals' end-study body weights, hemodynamic variables, and ICE measurements are shown for each group in Table 1. The end-study body weight was 89 [78–101] kg in the HFD group and only marginally greater than that in the control group (70 [66–91] kg, $P=0.3472$). The mean LA pressure tended to be higher in the HFD group than in the control group (34.5 [25.6–39.5] *vs.* 24.5 [21.3–27.8] mmHg, $P=0.0833$). There were no differences in other hemodynamic variables or the ICE measurements between the two groups. As expected, the following lipid levels were significantly higher in the HFD group than in the control group: total cholesterol (347 [191–434] mg/dL *vs.* 81 [67–88] mg/dl, $P=0.0088$), low-density lipoprotein cholesterol (LDL) (276 [115–340] mg/dL *vs.* 43 [34–48] mg/dL, $P=0.0163$) and high-